Donor natural killer (NK) cells as “veto” cells to promote donor-specific tolerance

Grant Award Details

Donor natural killer (NK) cells as “veto” cells to promote donor-specific tolerance

Grant Type: Transplantation Immunology

Grant Number: RM1-01724

Project Objective: The aim of this proposal was to find ways to improve the outcomes of treatments involving stem cell transplants by investigating the role of NK cells in rejection of allogeneic transplants. This proposal will seek to use donor-type activated NK cells to abrogate host rejection pathways.

Investigator:

Name:	William Murphy
Institution:	University of California, Davis
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Award Value: $1,257,601

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Donor natural killer (NK) cells as “veto” cells to promote donor-specific tolerance

Public Abstract: A major issue in the use of stem cells or in organ transplantation in general is the need to overcome graft rejection. Unfortunately, the only means currently available involves the use of systemic immunosuppression which leaves the recipient at risk for opportunistic infections. This proposal will seek to use the donor's immune cells to prevent rejection. Using a concept in which the donor immune cells (in this case, natural killer cells) are infused first, the recipient's immune cells will specifically seek to attack and reject it. The donor natural killer cells will be activated and thereby act as a "veto cell" and "attack the attacker" resulting in the eradication of only the host immune cells which would recognize the donor graft. Once eradicated, we will then infuse the donor stem cells which should now engraft without the need for extensive immunosuppression with the goal that the recipient will now become tolerant of the donor cells. This proposal will also examine the impact of recipient age on this process as the vast majority of patients in need of such therapy will be more advanced in age and this can impact both their rejection ability and the ability to suppress such rejection. These patients are also less able to handle the systemic immunosuppression so this can avoid these negative side-effects. Finally, the proposal will evaluate this "veto concept" in both mouse and human models which lends itself to immediate translation into the clinic. Use of these cells is already proceeding for the treatment of cancer. These studies thus will shed insights on using specific immune cell targeting with donor cells to remove the ability of the recipient to reject the graft but preserving immune functions to pathogens.

Statement of Benefit to California: This proposal will have significant impact and benefit to the State of California and its residents. The complications associated with systemic immunosuppression after transplantation are considerable and costly. In addition, there have been tremendous resources placed on the clinical use of stem cells. However, if there is rejection of these cells by the immune system or unacceptable toxicities due to life-long immunosuppression then the proposed stem cell therapies will not be translated to the clinic. Therefore, a final hurdle will be to safely and specifically abrogate the ability of the recipient to reject the graft. This proposal is eminently translatable to the clinic and would allow the use of the donor's own cells to specifically promote long-term engraftment. As such, this proposal will have an impact not only on stem cell transplantation but on solid organ transplantation as well.
